Suzuki–Miyaura Cross-Coupling of Amides by N–C Cleavage Mediated by Air-Stable, Well-Defined [Pd(NHC)(sulfide)Cl$_2$] Catalysts: Reaction Development, Scope and Mechanism

Shiyi Yang,[†] Xiang Yu,[†] Yaxu Liu ,[§] Michele Tomasini,[‡,⊥] Lucia Caporaso,[⊥] Albert Poater,[*,‡] Luigi Cavallo,[⊥,¶] Catherine S. J. Cazin,[§] Steven P. Nolan[*,§] and Michal Szostak[*,†]

[†] *Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States*

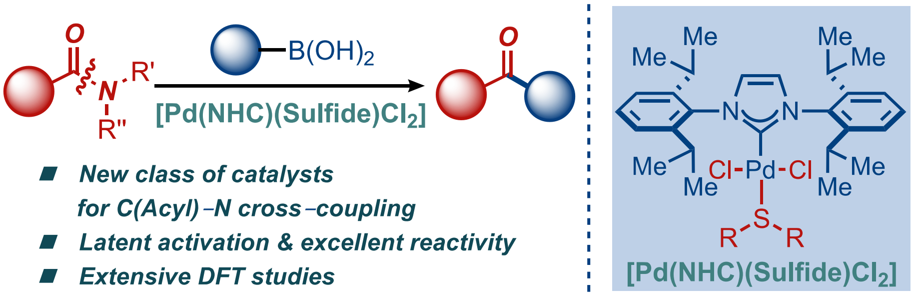
[‡] *Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, c/ Maria Aurèlia Capmany 69, Campus Montilivi, 17003 Girona, Catalonia, Spain*

[⊥] *Department of Chemistry, University of Salerno, Via Ponte don Melillo, 84084, Fisciano (SA), Italy*

[¶] *King Abdullah University of Science & Technology, KAUST Catalysis Center (KCC), 23955-6900 Thuwal, Saudi Arabia*

[§] *Department of Chemistry and Center for Sustainable Chemistry, Ghent University, Krijgslaan 281, S-3, B-9000 Ghent, Belgium*

Supporting Information



ABSTRACT: The Suzuki-Miyaura cross-coupling of amides by selective N–C acyl bond cleavage represents a powerful tool for constructing biaryl ketones from historically inert amide bonds. These amide bond activation reactions hinge upon efficient oxidative addition of the N–C acyl bond to Pd(0), however, in contrast to the well-researched activation of aryl halides by C(sp^2)–X oxidative addition, very few studies on the mechanism of C(acyl)–N bond oxidative addition and catalyst effect have been reported. Herein, we report a study on [Pd(NHC)(sulfide)Cl$_2$] catalysts in amide N–C bond activation. These readily prepared, well-defined, air- and moisture-stable Pd(II)–NHC catalysts feature SMe$_2$ (DMS = dimethylsulfide) or S(CH$_2$CH$_2$)$_2$ (THT = tetrahydrothiophene) as ancillary ligands. The reaction development, kinetic studies and reaction scope are presented. Extensive DFT studies were conducted to gain insight into the mechanism of C(acyl)–N bond oxidative addition and catalyst activation. We expect that [Pd(NHC)(sulfide)Cl$_2$] precatalysts featuring sulfides as well-defined, readily accessible ancillary ligands will find application in C(acyl)–X bond activation in organic synthesis and catalysis.

1. Introduction

In the past five years, tremendous progress has been achieved in activation of amide bonds by transition metals.[1-3] Once regarded as chemically inert due to the amide resonance ($n_N \rightarrow \pi^*_{C=O}$ barrier to rotation, 15-20 mol/kcal),[4] the activation of amide N–C acyl bonds has experienced a paradigm shift through ground-state-destabilization mechanism[5] that enables amides to participate in a broad range of generic cross-coupling reactions under mild conditions (Figure 1a).[1,2] This amide bond reactivity platform has captured significant attention due to the prevalence of amides in drug discovery research, agrochemistry, natural products, organic materials and biochemistry, where amides constitute the most common functional groups across various facets of academic and industrial research.[6,7]

The activation of amide C(acyl)–N bonds hinges upon efficient oxidative addition of the N–C acyl bond to Pd(0) (Figure 1a, box),[1] however, in contrast to the well-researched activation of aryl halides by C(sp^2)–X oxidative addition, very few studies focusing on the mechanism of C(acyl)–N bond oxidative addition and catalyst effect have been reported. While early studies used Pd–phosphine and Ni–NHC catalysts for amide bond activation,[8-10] later research has demonstrated that Pd–NHC complexes represent a privileged class of catalysts for amide N–C bond activation.[1,4,11]

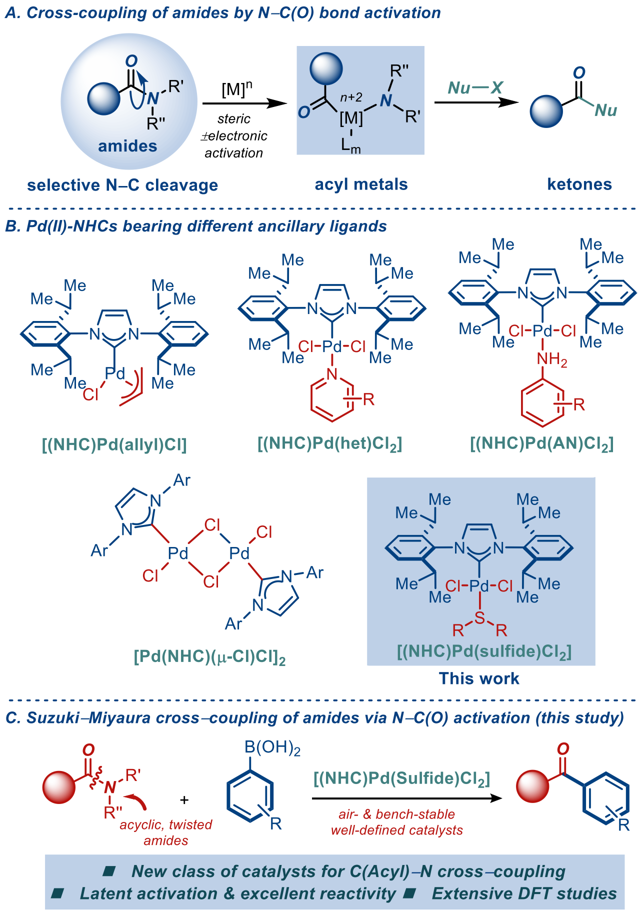


Figure 1. (a) Cross-coupling of amides by N–C(O) bond activation; (b) Pd(II)–NHCs bearing different ancillary ligands; (c) this study: Suzuki-Miyaura cross-coupling of amides via N–C(O) activation using $[Pd(NHC)(sulfide)Cl_2]$ complexes.

This class of catalysts heavily benefits from the availability of well-defined, air- and moisture-stable Pd(II)–NHC precursors, which render amide bond cross-coupling operationally-simple and applicable for a broad range of chemists.[11,12] The strong σ-donation and availability of various NHC ligands with differentiated steric properties facilitate oxidative addition of the C(acyl)–N amide bonds. The well-established functional group tolerance and broad applicability of Pd catalysis in cross-coupling enables to expand the scope of the reactions to more sensitive amide bonds using Pd(II)–NHCs.[11,12] To date, several classes of Pd(II)–NHCs bearing different ancillary throw-away ligands[13] enabling activation to catalytically-active monoligated NHC–Pd(0) have been established as effective in amide bond cross-coupling, including allyl-based ligands,[14] heterocycle-based ligands,[15] aniline-based ligands[16] and halide-bridged dimers,[17] such as [(NHC)Pd(R-allyl)Cl], $[(NHC)Pd(het)Cl_2]$, $[(NHC)Pd(AN)Cl_2]$, $[(NHC)Pd(\mu\text{-}Cl)Cl]_2$.[14–17] To ensure broad applicability of amide bond cross-coupling, it is imperative that new classes of catalysts be identified and the mechanism of oxidative addition of C(acyl)–N amide bonds investigated (Figure 1b).

Herein, we report a study on $[Pd(NHC)(sulfide)Cl_2]$ complexes in amide N–C bond activation (Figure 1C). These readily prepared, well-defined, air- and moisture-stable Pd(II)–NHC complexes feature SMe_2 (DMS = dimethylsulfide) and $S(CH_2CH_2)_2$ (THT = tetrahydrothiophene) as ancillary ligands.[18] The reaction development, kinetic studies and reaction scope are presented. The catalysts display latency in cross-coupling.[19] Extensive density functional theory (DFT) studies were conducted to gain insight into the mechanism of C(acyl)–N bond oxidative addition and catalyst activation in the cross-coupling. We expect that $[Pd(NHC)(sulfide)Cl_2]$ precatalysts featuring sulfides as well-defined, readily accessible ancillary ligands will find application in C(acyl)–X bond activation in organic synthesis and catalysis.

2. Results and Discussion

Design. Considering the key effect of stabilizing ancillary ligands in Pd(II)–NHC precatalysts observed in previous studies by our groups,[11–14,18] we were attracted to Pd(II)–NHC complexes bearing *S*-stabilizing ligands.

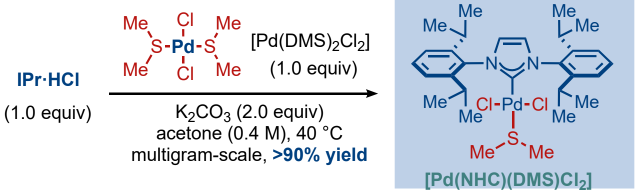
In general, there are several factors that should be considered when designing new well-defined Pd(II)–NHC catalysts for cross-coupling. In most cases, the activity is a balance between the catalyst stability, rate of activation, accessibility of anologues with different ancillary ligands, ease of synthesis and stabilization of the catalytically-active monoligated Pd(0)–NHC by recoordination of the ancillary ligand. In this conext, the most reactive Pd(II)–NHC catalysts discovered to date are suppored by bridged chloro dimers, $[(IPr)Pd(\mu\text{-}Cl)Cl]_2$, while the catalysts supported by allyl ligands, [(IPr)Pd(cin)Cl], are more stable. Furthermore, catalysts supported by heterocycles, $[(IPr)Pd(3\text{-}Cl\text{-}py)Cl_2]$, $[(IPr)Pd(AN)Cl_2]$, activate less readily, however, they benefit from the ease of synthesis and re-coordination of the nitrogen ligands to Pd(0).[14–17]

To ensure the broad applicability of Pd(II)–NHC complexes for cross-coupling, catalysts must be easy to prepare, have low cost of a possibly modular assembly and be air-stable. In the domain of Pd(II)–NHCs, the stabilization is afforded by the ancillary throw-away ligand, which should be readily removed during the activation step to Pd(0)–NHC, yet provide high bench- and air-stability of Pd(II)–NHC complexes.[11,12] $[Pd(NHC](sulfide)Cl_2]$ complexes bearing DMS and THT ligands are readily prepared from NHC salts and $Pd(sulfide)Cl_2$ using K_2CO_3 as a weak base on gram scale (Scheme 1).[18] DMS and THT are broadly available from the industrial synthesis on scale as scenting materials.

Our initial optimization is summarized in Table 1. *N*-Boc/Ph amide was selected as a model substrate because this class of ground-state-destabilized amides enables direct activation of common 1° and 2° amides through site selective *N-tert*-butoxycarboxylation of benzamides.[1a,b] This class of amides features decreased amidic resonance (RE = 7.2 kcal/mol, RE = resonance energy) in the presence of moderate twisting of amide bond (τ = 29.1°; χ_N = 8.4°, Winkler-Dunitz distortion, τ = twist angle, χ_N = N pyramidalization angle). The acyl Suzuki cross-coupling has been selected as a model reaction due to the importance of biaryl ketone products in organic synthesis and the availability of protocols enabling comparison of the reactivity with the present class of catalysts.[17]

[Pd(NHC)(sulfide)Cl_2] complexes bearing IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as NHC ligand and DMS and THT as sulfide ancillary ligands were selected for the initial screening (Chart 1). In addition, we screened a more sterically-demanding NHC analogue, IPr*, bearing 2,6-bis(benzhydryl) substitution (IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) to test the effect of the increased steric bulk on the oxidative addition of the C(acyl)–N amide bond, whereas it is known that the steric environment of acyl-metals is more sensitive to changes than C(sp^2)-metal centers.[11,12]

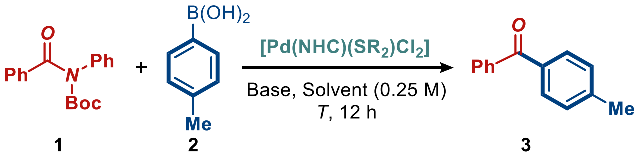
Scheme 1. Facile Synthesis of [Pd(NHC](sulfide)Cl_2] Complexes



Optimization Studies. We identified conditions using K_2CO_3 as a mild carbonate base, in THF as a solvent at 60 °C that promoted the cross-coupling in 82% yield using 0.5 mol% [Pd(IPr)(DMS)Cl_2] as catalyst (Table 1, entry 1). Interestingly, the THT congener, [Pd(IPr)(THT)Cl_2], showed comparable albeit slightly lower reactivity under these conditions (Table 1, entry 2), while the bulky [Pd(IPr*)(DMS)Cl_2] was completely unreactive (Table 1, entry 3). We further established that temperature is a critical factor, with no reaction taking place at 40 °C (Table 1, entry 4), while a modest improvement in yield was observed at 80 °C (Table 1, entry 5).

This finding suggests that 60 °C is required for catalyst activation, which is an important aspect of Pd(II)–NHC precatalyst stability. Furthermore, initial screening of the effect of catalyst loading indicated that a modest increase of the reaction efficiency is observed at 1 mol% with [Pd(IPr)(DMS)Cl_2] and [Pd(IPr)(THT)Cl_2] catalysts, while [Pd(IPr*)(DMS)Cl_2] was unreactive (Table 1, entries 6-9). Importantly, we next established that the addition of water significantly improves the reaction efficiency (Table 1, entries 10-11). Under these modified conditions, the reaction yield is close to quantitative using [Pd(IPr)(DMS)Cl_2] at 60 °C (Table 1, entry 10), while the reactivity initiates at 40 °C (Table 1, entry 11 cf. entry 4). This suggests that water aids in [Pd(IPr)(DMS)Cl_2] activation to monoligated Pd(0)–NHC. Extensive screening of various bases revealed that KF, Rb_2CO_3 and K_3PO_4 promote the cross-coupling, albeit in lower yields than K_2CO_3, while other bases, such as Cs_2CO_3, Na_2CO_3, KOAc and $KHCO_3$ are less effective (Table 1, entries 12-18). We next evaluated different solvents and established that DME, dioxane, toluene, MeCN and EtOH were less effective (Table 1, entries 19-22), while EtOAc, and in particular, 2-MeTHF gave optimal results (Table 1, entries 23-24), likely due to better solubility of K_2CO_3 in 2-MeTHF than in THF. It is noteworthy that both of these solvents are considered environmentally-friendly and sustainable by green chemistry principles, which is an important finding considering [Pd(NHC](sulfide)Cl_2] precatalysts for amide N(acyl)–C activation.[1,6,7]

Table 1. Optimization of the Reaction Conditions[a]



Entry	[Pd] catalyst	[Pd] loading (mol%)	Base	Solvent	T (°C)	Yield (%)
1[b]	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	THF	60	82
2	[Pd(IPr)(THT)Cl_2]	0.5	K_2CO_3	THF	60	80
3	[Pd(IPr*)(DMS)Cl_2]	0.5	K_2CO_3	THF	60	0
4	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	THF	40	0
5	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	THF	80	87
6	[Pd(IPr)(DMS)Cl_2]	0.25	K_2CO_3	THF	60	15
7	[Pd(IPr)(DMS)Cl_2]	1.0	K_2CO_3	THF	60	85
8	[Pd(IPr)(THT)Cl_2]	1.0	K_2CO_3	THF	60	84
9	[Pd(IPr*)(THT)Cl_2]	1.0	K_2CO_3	THF	60	0
10[b]	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	THF	40	24
11[b]	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	THF	60	97
12	[Pd(IPr)(DMS)Cl_2]	0.5	Cs_2CO_3	THF	60	17
13	[Pd(IPr)(DMS)Cl_2]	0.5	Na_2CO_3	THF	60	8
14	[Pd(IPr)(DMS)Cl_2]	0.5	Rb_2CO_3	THF	60	38
15	[Pd(IPr)(DMS)Cl_2]	0.5	KF	THF	60	62
16	[Pd(IPr)(DMS)Cl_2]	0.5	K_3PO_4	THF	60	35
17	[Pd(IPr)(DMS)Cl_2]	0.5	KOAc	THF	60	<2
18	[Pd(IPr)(DMS)Cl_2]	0.5	$KHCO_3$	THF	60	<2
19	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	DME	60	10
20	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	Dioxane	60	25
21	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	Toluene	60	39
22	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	MeCN	60	<2
23	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	EtOH	60	<2
24	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	EtOAc	60	79
25	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	2-MeTHF	60	95
26[b]	[Pd(IPr)(DMS)Cl_2]	0.5	K_2CO_3	2-MeTHF	60	>98
27[b]	[Pd(IPr)(DMS)Cl_2]	0.25	K_2CO_3	2-MeTHF	60	>98
28[b]	[Pd(IPr)(DMS)Cl_2]	0.1	K_2CO_3	2-MeTHF	60	98
29[b]	[Pd(IPr)(DMS)Cl_2]	0.25	K_2CO_3	2-MeTHF	40	88
30[b]	[Pd(IPr)(DMS)Cl_2]	0.25	K_2CO_3	2-MeTHF	23	<2
31	[Pd(IPr)(DMS)Cl_2]	0.25	K_2CO_3	2-MeTHF	60	68
32[b]	[Pd(IPr)(THT)Cl_2]	0.1	K_2CO_3	2-MeTHF	60	95
33[b]	[Pd(IPr*)(DMS)Cl_2]	0.1	K_2CO_3	2-MeTHF	60	0

[a] Conditions: amide **1a** (1.0 equiv), 4-Tol-B$(OH)_2$ (2.0 equiv), base (3.0 equiv), [Pd] (0.10-0.5 mol%), solvent (0.25 M), *T*, 12 h. [b] water (5.0 equiv) as additive. SR_2 = DMS, THT (SMe_2, $S(CH_2CH_2)_2$); NHC = IPr, IPr*.

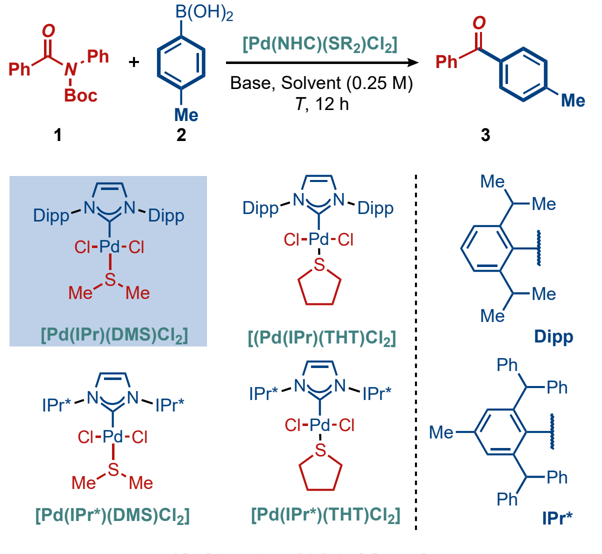
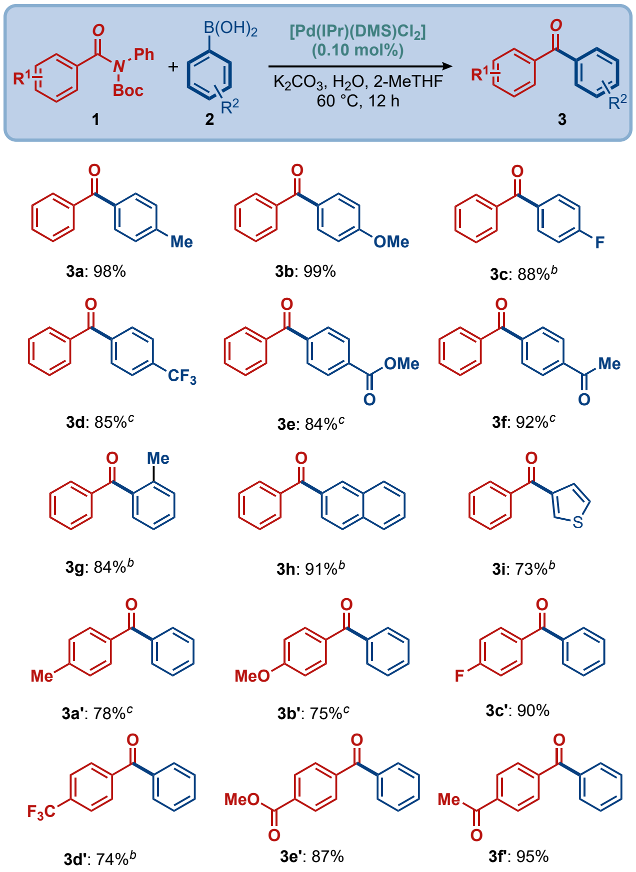


Chart 1. Structures of [Pd(NHC)(sulfide)Cl_2] catalysts.

Furthermore, the addition of water had a beneficial effect on the cross-coupling using 2-MeTHF, resulting in a major improvement in the reaction efficiency (Table 1, entries 26-28). Under these conditions the cross-coupling proceeded in a close to quantitative yield at 0.1 mol% catalyst loading (Table 1, entry 28). Moreover, the reaction is initiated at 40 °C in high yield (Table 1, entry 29), suggesting that catalyst activation and/or transmetallation are more facile under these conditions. Note, however, that no reaction takes place at 23 °C (Table 1, entry 30). It is also instructive to compare the reaction efficiency at 0.25 mol% Pd loading under anhydrous conditions in 2-MeTHF (Table 1, entry 31) vs. THF (Table 1, entry 6), indicating the beneficial effect of 2-MeTHF on the amide C(acyl)–N cross-coupling using [Pd(NHC](sulfide)Cl_2], which could be useful for amide electrophiles that require strictly anhydrous conditions.

Finally, we established that [Pd(IPr)(THT)Cl_2] also leads to high conversion in 2-MeTHF, while [Pd(IPr*)(DMS)Cl_2] was unreactive (Table 1, entries 32-33). This permits to establish the order of reactivity as [Pd(IPr)(DMS)Cl_2] > [Pd(IPr)(THT)Cl_2] >> [Pd(IPr*)(DMS)Cl_2].

Scheme 2. Scope of the Suzuki-Miyaura Cross-Coupling of Amides by [Pd(IPr)(DMS)Cl_2] Catalysis[a]



[a]Conditions: amide (1.0 equiv), Ar-B$(OH)_2$ (2.0 equiv), K_2CO_3 (3.0 equiv), [Pd] (0.10 mol%), H_2O (5 equiv), 2-MeTHF (0.25 M), 60 °C, 12 h. [b][Pd] (0.25 mol%). [c][Pd] (0.50 mol%). See SI for details.

Scope Studies. With the optimized conditions in hand, the scope of the Suzuki-Miyaura cross-coupling was briefly investigated (Scheme 2). We used [Pd(IPr)(DMS)Cl_2] at 0.1 mol% loading, while in select cases the loading was increased to 0.25 or 0.5 mol% to ensure full conversion. We found that the scope of the amide cross-coupling using [Pd(IPr)(DMS)Cl_2] is broad and includes various arylboronic acids and benzamides. As such, electronic variation on the boronic acid component is readily compatible with the method, including electron-neutral (**3a**), electron-rich (**3b**) and electron-deficient boronic acids (**3c–3f**). Furthermore, steric hindrance (**3g**) is well-tolerated by this class of catalysts. Polyconjugated aromatic (**3h**) and heterocyclic boronic acids (**3i**) could be employed as well. Importantly, these conditions are fully-compatible with electrophilic functional groups, such as esters (**3e**) and ketones (**3f**) that would be problematic using traditional hard organometallic centers. In terms of benzamide scope, the cross-coupling is also compatible with electron-neutral (**3a'**), electron-rich (**3b'**) and electron-deficient amide electrophiles (**3c'–3f'**). Again, electrophilic functional groups are well-tolerated on the amide component, providing useful handles for functionalization (**3e'–3f'**). Overall, the scope of the cross-coupling mediated by [Pd(IPr)(DMS)Cl_2] compares well with other Pd(II)–NHC precatalysts,[11,12] while having the benefit of environmentally-friendly and sustainable 2-MeTHF as a reaction medium.[20]

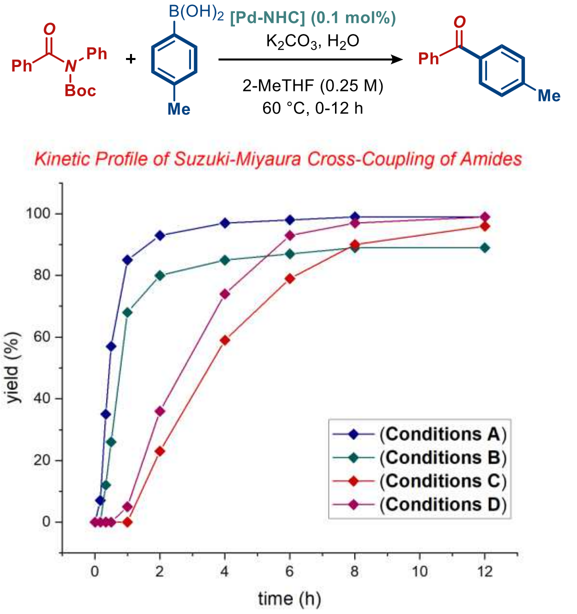


Figure 2. Kinetic studies of the Suzuki-Miyaura cross-coupling of amides using [Pd(NHC)$(SR_2)Cl_2$] precatalysts[a] [a]Conditions: amide (1.0 equiv), 4-Tol-B$(OH)_2$ (2.0 equiv), K_2CO_3 (3.0 equiv), [Pd] (0.10 mol%), H_2O (5 equiv), 2-MeTHF (0.25 M), 60 °C, 0-12 h. [Pd–NHC] = [Pd(IPr)(cin)Cl] (Conditions A), [Pd(IPr)(3-Cl-py)Cl_2] (Conditions B), [Pd(IPr)(THT)Cl_2] (Conditions C), [Pd(IPr)(DMS)Cl_2] (Conditions D). THT = $S(CH_2CH_2)_2$; DMS = SMe_2. See SI for details.

Kinetic Profiling Studies. We next conducted kinetic studies to investigate the effect of air- and bench-stable [Pd(IPr)$(SR_2)Cl_2$] complexes on amide C(acyl)–N coupling (Figure 2). Allyl-based and heterocycle-based complexes bearing the same IPr ligand, [Pd(IPr)(cin)Cl] and [Pd(IPr)(3-Cl-py)Cl_2] were selected for comparison. Interestingly, we found that both [Pd(IPr)$(SR_2)Cl_2$] catalysts, namely [Pd(IPr)(DMS)Cl_2] and [Pd(IPr)(THT)Cl_2] behave as latent precatalysts in the cross-coupling. Allyl- and heterocycle based catalysts, [Pd(IPr)(cin)Cl] and [Pd(IPr)(3-Cl-py)Cl_2] showed more facile activation to the active Pd(0)–

NHC under the developed conditions (1 h: [Pd(IPr)(cin)Cl], 85% yield; [Pd(IPr)(3-Cl-py)Cl$_2$], 68% yield), while [Pd(IPr)(DMS)Cl$_2$] and [Pd(IPr)(THT)Cl$_2$] gave no conversion (1 h: [Pd(IPr)(Me$_2$S)Cl$_2$], <5% yield; [Pd(IPr)(THT)Cl$_2$], <5% yield). However, after the initiation (1-2 h), both catalysts superpassed the heterocycle-based [Pd(IPr)(3-Cl-py)Cl$_2$] (12 h: [Pd(IPr)(DMS))Cl$_2$], [Pd(IPr)(THT)Cl$_2$], >95%), while the more reactive of the two [Pd(IPr)(DMS)Cl$_2$] matched the reactivity of the allyl-based [Pd(IPr)(cin)Cl] (12 h: [Pd(IPr)(DMS)Cl$_2$], >98%). Overall, the kinetic profiling clearly show latency and high stability of [Pd(IPr)(SR$_2$)Cl$_2$] catalysts, which may open the door for the development of latent protocols for cross-coupling. It should be noted that latent catalysts have attracted significant attention, especially in polymer chemistry, where an external stimulus, such as heat, light or chemical activation, permits for switching on the reactivity and controlling the onset of a catalytic process.[19] The order of reactivity observed in the kinetic profiling studies, [(IPr)Pd(μ-Cl)Cl] > [(IPr)Pd(cin)Cl] > [(IPr)Pd(3-Cl-py)Cl$_2$] > [Pd(IPr)(DMS)Cl$_2$] is consistent with the ease of activaton to the monoligated Pd(0)–NHC.[17a]

DFT Studies. Intrigued by the unusual profile of [Pd(IPr)(SR$_2$)Cl$_2$] catalysts, we conducted extensive DFT studies to gain insight into the mechanism of C(acyl)–N bond oxidative addition and catalyst effect of this class of catalysts, as well as in its pre-activation (Figure 3).

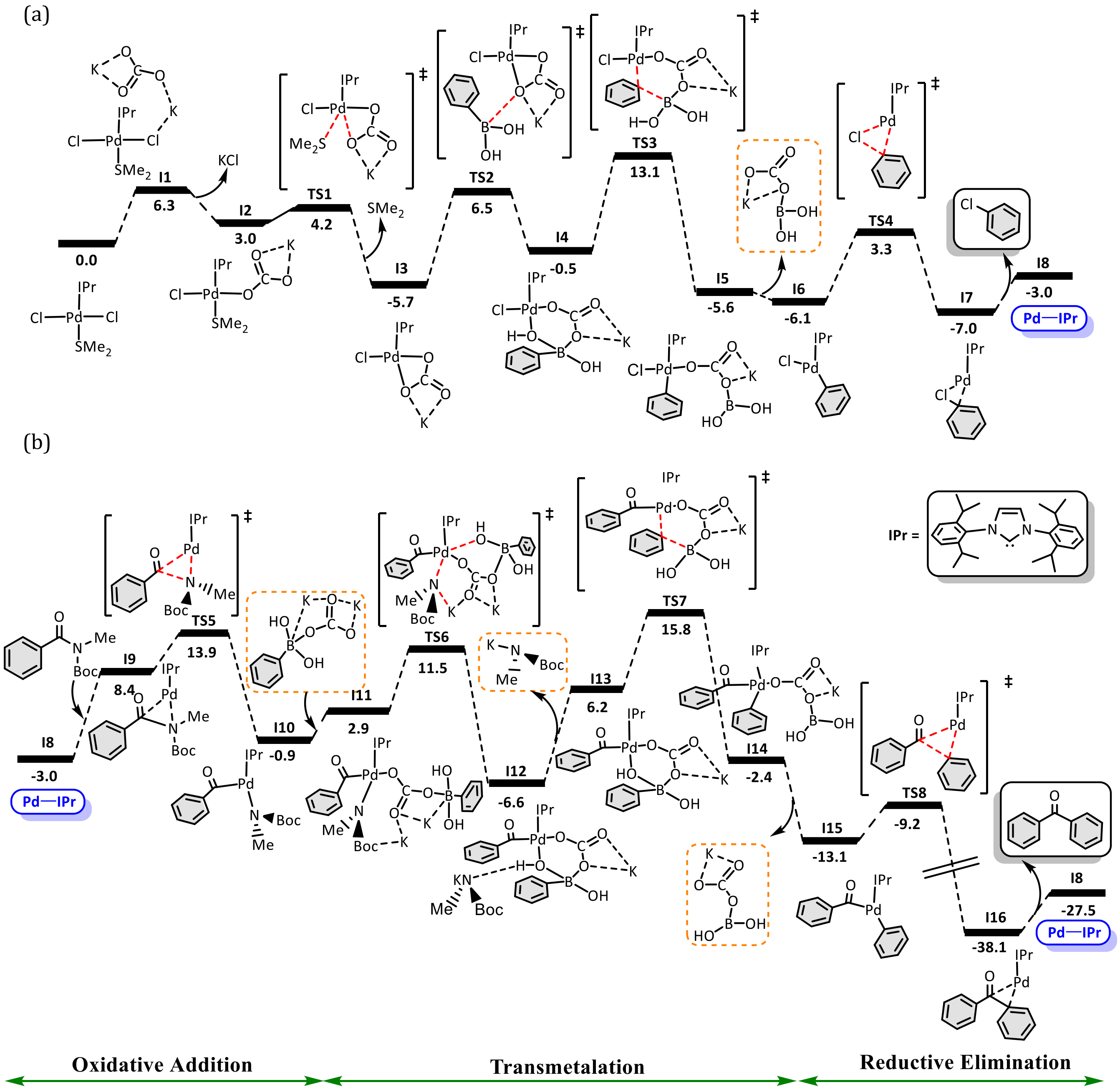


Figure 3. Reaction profile (relative Gibbs energies in kcal/mol, at the M06/Def2-TZVP~sdd (smd-THF)//BP86-D3/SVP~sdd level of theory) of (a) the activation of the Pd(IPr)SMe$_2$Cl$_2$ precatalyst and (b) Suzuki–Miyaura cross-coupling of amides by N–C Cleavage mediated by the Pd(IPr) catalytic active species (the red dotted lines indicate the bonds that break/form in the transition states).

First, the pre-catalyst exchanges a chloride ligand for KCO$_3$ releasing a molecule of KCl and then, SMe$_2$ is released overcoming a small barrier of 1.2 kcal/mol through to the transition state **TS1**, reaching the intermediate **I3** (5.7 kcal/mol below the precursor). Then, in two successive steps, the reagent PhB(OH)$_2$ succeeds in transferring the aryl to the metal center, to intermediate **I5**, overcoming two barriers of 12.2 and 13.6 kcal/mol. First there is the formation, of a B-O bond via **TS2**, involving one oxygen of the anionic KCO$_3$ moiety with the boronic acid, and subsequently the phenyl migrates from boron to palladium. Overall, both steps end up defining the rate determining state (rds) with a global barrier of only 18.8 kcal/mol.[21] From intermediate **I5**, K(CO$_3$)B(OH)$_2$ is easily dissociated. From the next intermediate **I6**, reductive elimination allows to release Ph-Cl into solution (overcoming a barrier of 9.4 kcal/mol through **TS4**). Finally, the resulting intermediate **I7** with PhCl and the metal weakly interacting each other releases PhCl to obtain the catalytically active Pd(0) species **I8**,[21b,22] relatively unstable, but still 3.0 kcal/mol lower in energy than the pre-catalyst.

It should be noted that the pathway by which SMe$_2$ is liberated was examined and also was the fact that it is released once a chloride has been exchanged for KCO$_3$, *i.e.* from intermediate **I2**. This makes the combination with a base the perfect scenario to address the formation of a Pd(0) species such as **I8**, which is fundamental in cross-coupling catalysis. In fact, the initial dissociative release of SMe$_2$ from the pre-catalyst has a kinetic cost of 20.7 kcal/mol since it requires overcoming a transition state, linked to a thermodynamic cost of 9.7 kcal/mol. Moreover, carrying out the process from an intermediate similar to **I4** but with SMe$_2$ bonded to palladium, has a kinetic cost of 17.7 kcal/mol, and likewise the unfavorable thermodynamics by 11.6 kcal/mol. Whether the SMe$_2$ group could transfer a methyl group to a chlorine was also examined but this process requires a kinetic cost greater than 40 kcal/mol in the most favorable case. On the other hand, we also focused on studying whether the reductive elimination, that is, the one described by **TS4**, can occur without the dissociation of the neutral K(CO$_3$)B(OH)$_2$ moiety so as to leave the metal partially protected. Although it would be thermodynamically favored by 3.0 kcal/mol, the kinetic barrier raises to a value of 23.1 kcal/mol, 19.4 kcal/mol more than when it occurs without K(CO$_3$)B(OH)$_2$.

Moving on to the catalytic cycle and following the previous insights,[21a] **I8** interacts with the amide in the intermediate **I9** as an adduct to break its C–N bond in the first step after overcoming **TS5** with a cost of 16.9 kcal/mol from **I8**. From intermediate **I10**, the boron reagent comes into play again after reacting with a base to form intermediate **I11**. The latter breaks the Pd–N bond facilitating the formation of a new bond between the metal and one hydroxyl group via **TS6**. The process requires 12.4 kcal/mol compared to **I10**. Next, from **I12**, there is the transfer of the aryl group from boron to palladium through **TS7**, but it is necessary to go through **I13** by first dissociating the newly dissociated amine together with a potassium atom. **TS7** would only have a barrier of 9.6 kcal/mol, but it must be taken into account as it is the rds and the kinetic cost of **I12** must be taken into account thus increasing this step to 22.4 kcal/mol. Thus, this is not only the rds of the catalytic cycle, but also taking into account the pre-activation, it is contrary to what is usually found for similar palladium systems, both monometallic[11e,21] and bimetallic,[17]. With phenyl on the metal, intermediate **I14** releases the neutral group K(CO$_3$)B(OH)$_2$ reaching intermediate **I15**, where, with a small barrier of only 3.9 kcal/mol, reductive elimination occurs to give rise to the ketone still attached to the metal as an adduct in **I16**. Once released, with an exoergonic thermodynamic cycle of 24.5 kcal/mol, the cost of closing the catalytic cycle in the **I8** species is then 10.6 kcal/mol. It should be mentioned that the entropic contribution is not taken into account *i.e.* omitting the corrections of entropy and standard state of 1 M concentration in solution.[23] Nevertheless, the resulting cost would still have to be considered in the following catalytic cycle,[24] and past benchmark studies led by some of us concluded that the M06/Def2-TZVP~sdd (smd-THF)//BP86-D3/SVP~sdd level of theory level of theory displays similar results.[25]

3. Conclusions

In summary, we have reported Suzuki-Miyaura cross-coupling of amides by N–C bond activation mediated by [Pd(NHC)(sulfide)Cl$_2$] complexes. These complexes represent a new class of readily prepared, air- and bench-stable catalysts for C(acyl)–N amide bond activation, where the stability is provided by sulfide ancillary ligands. The complexes show high reactivity in amide bond cross-coupling, enabling efficient Suzuki-Miyaura coupling at low catalyst loading. These complexes operate in environmentally-friendly and sustainable 2-MeTHF as a reaction solvent. An important feature is the latency exhibited by [Pd(NHC)(sulfide)Cl$_2$] complexes, which could be exploited in synthetic protocols for bond activation.[19] Extensive DFT studies provide insight into the mechanism of C(acyl)–N oxidative addition and catalyst activation pathways.

The catalyst stands out for the simplicity in its activation, confirming again that it is not only necessary to focus efforts on the catalytic cycle, but on pre-activation, especially for cross coupling reactions. Furthermore, here the symbiosis between the leaving group SMe$_2$ and the base has been verified computationally. We anticipate that sulfide-based Pd(II)–NHC catalysts will find further applications in C(acyl)–X bond activation in organic synthesis and catalysis.

4. Experimental Section

General Methods. All compounds reported in the manuscript have been previously described in literature or prepared by the method reported previously unless stated otherwise. All boronic acids are commercially available and have been purchased from Oakwood Chemical. All experiments involving palladium were performed using standard Schlenk techniques under nitrogen or argon unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by distillation from sodium/benzophenone under nitrogen. All solvents were deoxygenated prior to use. All other chemicals were purchased at the highest commercial grade and used as received. All other general methods have been published.[17a] ^{1}H NMR and ^{13}C NMR data are given for all compounds in the Supporting Experimental for characterization purposes. ^{1}H NMR, ^{13}C NMR and HRMS data are reported for all new compounds. Note: It should be noted that small-size sulfur compounds posses a characteristic smell. We have not observed any issues during the synthesis. However, care should be taken when handling odorants in well-ventillated fume hoods.[18] All amides used in this study were prepared by procedures reported in the literature.[17] [(IPr)Pd(cin)Cl] and [Pd(IPr)(3-Cl-py)Cl_2] precatalysts used in this study were purchased from Sigma-Aldrich. [Pd(NHC)(sulfide)Cl_2] precatalysts used in this study were prepared according to the established procedure.[18]

General Procedure for Optimization of the Reaction Conditions. An oven-dried vial equipped with a stir bar was charged with amide **1a** (1.0 equiv), boronic acid (typically, 2.0 equiv), base (typically, 3.0 equiv), [Pd(NHC)(sulfide)Cl_2] (x mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Solvent (typically, 0.25 M) and H_2O (as indicated) were added with vigorous stirring at room temperature. After stirring for 12 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

General Procedure for the Suzuki-Miyaura Cross-Coupling of Amides by [Pd(NHC)(sulfide)Cl_2] Catalysis. An oven-dried vial equipped with a stir bar was charged with amide (1.0 equiv), boronic acid (2.0 equiv), potassium carbonate (3.0 equiv), [Pd(NHC)(sulfide)Cl_2] catalyst (as indicated), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (typically, 0.25 M) and H_2O (5 equiv) were added at room temperature and the reaction was vigorously stirred at 60 ºC in an oil bath. After 12 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Procedure for the Suzuki-Miyaura Cross-Coupling of Amides by [Pd(NHC)(sulfide)Cl_2] Catalysis. 1.0 Mmol Scale. An oven-dried vial equipped with a stir bar was charged with *tert*-butyl benzoyl(phenyl)carbamate (297.4 mg, 1.0 mmol, 1.0 equiv), 4-tolylboronic acid (271.9 mg, 2.0 mmol, 2.0 equiv), potassium carbonate (414.6 mg, 3.0 mmol, 3.0 equiv), [Pd(IPr)(DMS)Cl_2] (0.1 mol%, 0.65 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (4.0 mL, 0.25 M) and H_2O (90 mg, 5.0 mmol, 5.0 equiv) were added at room temperature and the reaction was vigorously stirred at 60 ºC in an oil bath. After 12 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes = 1:10) afforded the title product. Yield 98%, 192.9 mg. Characterization data are included in the section below.

Characterization Data of the Cross-Coupling Products

Phenyl(4-tolyl)methanone (3a). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), 4-tolylboronic acid (0.40 mmol, 54.4 mg), K_2CO_3 (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl_2] (0.1 mol%, 0.13 mg) and H_2O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3a** in 98% yield (38.5 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 2.45 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 196.5, 143.3, 138.0, 134.9, 132.2, 130.3, 130.0, 129.0, 128.2, 21.7. The spectral data matched literature values.[26]

(4-Methoxyphenyl)(phenyl)methanone (3b). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), (4-methoxyphenyl)boronic acid (0.40 mmol, 60.8 mg), K_2CO_3 (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl_2] (0.1 mol%, 0.13 mg) and H_2O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3b** in 99% yield (42.2 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.9 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.60 – 7.53 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 195.6, 163.2, 138.3, 132.6, 131.9, 130.2, 129.7, 128.2, 113.6, 55.5. The spectral data matched literature values.[26]

(4-Fluorophenyl)(phenyl)methanone (3c). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), (4-fluorophenyl)boronic acid (0.40 mmol, 56.0 mg), K_2CO_3 (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl_2] (0.25 mol%, 0.32 mg) and H_2O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3c** in 88% yield (35.2 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.81 – 7.74 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 8.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 195.3, 165.4 (d, *J* = 254.2 Hz), 137.5, 133.8 (d, *J* = 3.1 Hz), 132.7 (d, *J* = 9.1 Hz), 132.5, 129.9, 128.4, 115.5 (d, *J* = 21.8 Hz). The spectral data matched literature values.[26]

Phenyl(4-(trifluoromethyl)phenyl)methanone (3d). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), (4-(trifluoromethyl)phenyl)boronic acid (0.40 mmol, 76.0 mg), K_2CO_3 (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl_2] (0.5 mol%, 0.64 mg) and H_2O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3d** in 85% yield (42.8 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.81 (dd, *J* = 8.2, 1.3 Hz, 3H), 7.76 (d, *J* = 8.1

Hz, 3H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 195.6, 140.7, 136.7, 133.8 (d, *J* = 32.7 Hz), 130.2, 130.1, 128.5, 125.4 (q, *J* = 3.8 Hz), (q, *J* = 277.2 Hz). The spectral data matched literature values.[26]

Methyl 4-benzoylbenzoate (3e). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), (4-(methoxycarbonyl)phenyl)boronic acid (0.40 mmol, 72.0 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.5 mol%, 0.64 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3e** in 84% yield (40.3 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15 (d, *J* = 8.2 Hz,2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 0.8 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 196.1, 166.3, 141.3, 137.0, 133.2, 133.0, 130.1, 129.8, 129.5, 128.5, 52.5. The spectral data matched literature values.[26]

1-(4-Benzoylphenyl)ethan-1-one (3f). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), (4-acetylphenyl)boronic acid (0.40 mmol, 65.6 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.5 mol%, 0.64 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:8) the title compound **3f** in 92% yield (41.4 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.81 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.63 (ddt, *J* = 7.9, 7.0, 1.3 Hz, 1H), 7.56 – 7.46 (m, 2H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 197.5, 196.0, 141.4, 139.6, 136.9, 133.0, 130.1, 130.1, 128.5, 128.2, 26.9. The spectral data matched literature values.[26]

Phenyl(2-tolyl)methanone (3g). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), 2-tolylboronic acid (0.40 mmol, 54.4 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.25 mol%, 0.32 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3g** in 84% yield (32.8 mg). Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.39 (td, *J* = 7.5, 1.6 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.27 – 7.22 (m, 1H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 198.7, 138.6, 137.8, 136.8, 133.1, 131.0, 130.2, 130.1, 128.5, 128.5, 125.2, 20.0. The spectral data matched literature values.[26]

Naphthalen-2-yl(phenyl)methanone (3h). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), naphthalen-2-ylboronic acid (0.40 mmol, 68.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.25 mol%, 0.32 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3h** in 91% yield (42.4 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.27 (s, 1H), 7.95 (d, *J* = 1.2 Hz, 2H), 7.92 (dd, *J* = 8.0, 3.3 Hz, 2H), 7.87 (d, *J* = 6.8 Hz, 2H), 7.66 – 7.59 (m, 2H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 196.8, 137.9, 135.3, 134.9, 132.4, 132.3, 131.9, 130.1, 129.4, 128.4, 128.3, 128.3, 127.8, 126.8, 125.8. The spectral data matched literature values.[26]

Phenyl(thiophen-3-yl)methanone (3i). According to the general procedure, the reaction of **1a** (0.20 mmol, 59.5 mg), thiophen-3-ylboronic acid (0.40 mmol, 51.2 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.25 mol%, 0.32 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3i** in 73% yield (27.5 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.85 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.39 (dd, *J* = 5.0, 2.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 190.0, 141.3, 138.7, 133.9, 132.3, 129.4, 128.6, 128.4, 126.2. The spectral data matched literature values.[27]

Phenyl(4-tolyl)methanone (3a'). According to the general procedure, the reaction of **1b** (0.20 mmol, 62.2 mg), phenylboronic acid (0.40 mmol, 48.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.5 mol%, 0.64 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3a'** in 78% yield (30.7 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 – 7.76 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 196.5, 143.3, 138.0, 134.9, 132.2, 130.3, 129.9, 129.0, 128.2, 21.7. The spectral data matched literature values.[26]

(4-Methoxyphenyl)(phenyl)methanone (3b'). According to the general procedure, the reaction of **1c** (0.20 mmol, 65.4 mg), phenylboronic acid (0.40 mmol, 48.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.5 mol%, 0.64 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3b'** in 75% yield (31.8 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, *J* = 8.9 Hz, 2H), 7.76 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 195.6, 163.2, 138.3, 132.6, 131.9, 130.2, 129.7, 128.2, 113.6, 55.5. The spectral data matched literature values.[26]

(4-Fluorophenyl)(phenyl)methanone (3c'). According to the general procedure, the reaction of **1d** (0.20 mmol, 63.0 mg), phenylboronic acid (0.40 mmol, 48.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.1 mol%, 0.13 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3c'** in 90% yield (35.9 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.77 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 8.6 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 195.3, 165.4 (d, *J* = 254.0 Hz), 137.5, 133.82 (d, *J* = 3.1 Hz), 132.7 (d, *J* = 9.1 Hz), 132.5, 129.9, 128.4, 115.47 (d, *J* = 21.8 Hz). The spectral data matched literature values.[26]

Phenyl(4-(trifluoromethyl)phenyl)methanone (3d'). According to the general procedure, the reaction of **1e** (0.20 mmol, 73.0 mg), phenylboronic acid (0.40 mmol, 48.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.25 mol%, 0.32mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3d'** in 74% yield (37.2 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.81 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 195.6, 140.7, 136.8, 133.8 (d, *J* = 32.6 Hz), 133.1, 130.2, 130.1, 128.5, 125.4 (q, *J* = 3.8 Hz), 123.7 (d, *J* = 272.3 Hz). The spectral data matched literature values.[26]

Methyl 4-benzoylbenzoate (3e'). According to the general procedure, the reaction of **1f** (0.20 mmol, 71.6 mg), phenylboronic acid (0.40 mmol, 48.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.1 mol%, 0.13 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:10) the title compound **3e'** in 87% yield (41.8 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.82 – 7.79 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 196.1, 166.3, 141.3, 137.0, 133.2, 133.0, 130.1, 129.8, 129.5, 128.5, 52.5. The spectral data matched literature values.[26]

1-(4-Benzoylphenyl)ethan-1-one (3f'). According to the general procedure, the reaction of **1g** (0.20 mmol, 67.8 mg), phenylboronic acid (0.40 mmol, 48.8 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.1 mol%, 0.13 mg) and H$_2$O (5.0 equiv, 18 mg) in 2-MeTHF (0.25 M, 0.8 mL) for 12 h at 60 ºC in an oil bath, afforded after filtration and chromatography (EtOAc/hexanes = 1:8) the title compound **3f'** in 95% yield (42.6 mg). White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 7.1 Hz, 2H), 7.66 – 7.59 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 197.5, 196.0, 141.4, 139.6, 136.9, 133.0, 130.1, 130.1, 128.5, 128.2, 26.9. The spectral data matched literature values.[6]

General Procedures for Kinetic Studies

Conditions A. An oven-dried vial equipped with a stir bar was charged with amide **1a** (0.2 mmol), 4-methylphenyl boronic acid (0.40 mmol, 54.4 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(cin)Cl] (0.1 mol%, 0.14 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (0.25 M, 0.8 mL) and H$_2$O (5.0 equiv, 18 mg) were added with vigorous stirring and the vial was placed in an oil bath preheated to 60 °C. After the indicated time the reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR (CDCl$_3$, 500 MHz) and GC-MS to obtain yield using internal standard and comparison with authentic sample **3a**. Two groups of 9 parallel reactions were run and stopped at 10 min, 20 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 12 h.

Conditions B. An oven-dried vial equipped with a stir bar was charged with amide **1a** (0.2 mmol), 4-methylphenyl boronic acid (0.40 mmol, 54.4 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [Pd(IPr)(3-Cl-py)Cl$_2$] (0.1 mol%, 0.14 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (0.25 M, 0.8 mL) and H$_2$O (5.0 equiv, 18 mg) were added with vigorous stirring and the vial was placed in an oil bath preheated to 60 °C. After the indicated time the reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR (CDCl$_3$, 500 MHz) and GC-MS to obtain yield using internal standard and comparison with authentic sample **3a**. Two groups of 9 parallel reactions were run and stopped at 10 min, 20 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 12 h.

Conditions C. An oven-dried vial equipped with a stir bar was charged with amide **1a** (0.2 mmol), 4-methylphenyl boronic acid (0.40 mmol, 54.4 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(THT)Cl$_2$] (0.1 mol%, 0.13 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (0.25 M, 0.8 mL) and H$_2$O (5.0 equiv, 18 mg) were added with vigorous stirring and the vial was placed in an oil bath preheated to 60 °C. After the indicated time the reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR (CDCl$_3$, 500 MHz) and GC-MS to obtain yield using internal standard and comparison with authentic sample **3a**. Two groups of 9 parallel reactions were run and stopped at 10 min, 20 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 12 h.

Conditions D. An oven-dried vial equipped with a stir bar was charged with amide **1a** (0.2 mmol), 4-methylphenyl boronic acid (0.40 mmol, 54.4 mg), K$_2$CO$_3$ (0.60 mmol, 82.8 mg), [(IPr)Pd(DMS)Cl$_2$] (0.1 mol%, 0.13 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (0.25 M, 0.8 mL) and H$_2$O (5.0 equiv, 18 mg) were added with vigorous stirring and the vial was placed in an oil bath preheated to 60 °C. After the indicated time the reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR (CDCl$_3$, 500 MHz) and GC-MS to obtain yield using internal standard and comparison with authentic sample **3a**. Two groups of 9 parallel reactions were run and stopped at 10 min, 20 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 12 h.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and it's Supporting Information.

Supporting Information

^{1}H and ^{13}C NMR spectra, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

albert.poater@udg.edu
steven.nolan@ugent.be
michal.szostak@rutgers.edu

Notes

The authors declare no competing financial interest.

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